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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,772	04/07/2006	Atsushi Miyawaki	P28025	6795
7055 7590 10/16/2008 GREENBLUM & BERNSTEIN, P.L.C. 1950 ROLAND CLARKE PLACE RESTON, VA 20191				
EXAMINER LEE, JAE W				
ART UNIT		PAPER NUMBER		
1656				
NOTIFICATION DATE		DELIVERY MODE		
10/16/2008		ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/538,772

Applicant(s)

MIYAWAKI ET AL.

Examiner

JAE W. LEE

Art Unit

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 June 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) 1-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/CDC)
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date: _____

DETAILED ACTION

Application status

In response to the previous Office action, a non-Final rejection (mailed on 08/17/2007), Applicants filed a response and amendment received on 06/05/2008. Said amendment amended Claims 21 and 23. Thus, Claims 21-23 are at issue and present for examination.

Applicants' arguments filed on 06/05/2008, have been fully considered, and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

It is noted by the Examiner that Claims 1-20 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention in the previous Office actions, a non-Final rejection (mailed on 08/17/2007).

Claim Objections

Claims 21 and 23 are objected to because of the following informalities:

The previous objection of Claims 21-23 for depending from a non-elected claim, i.e., claim 1, is withdrawn by virtue of Applicants' amendment.

Claim 21 is objected to because the recitation of "A nucleic acid encoding a fluorescent indicator," which can be substantially improved with respect to form because nucleic acids do not encode indicators but rather a polypeptide or a protein.

Claim 21 is objected to because the recitation of "which indicator comprises" can be substantially improved with respect to form (see line 2 of claim 21). The Examiner suggests replacing the noted phrase with ---which comprises---.

Claim 23 is objected to because the recitation of "transformant" can be improved form. Since the term "transformant," without "cell" following the term, encompasses in its broadest reasonable interpretation, multicellular organisms (i.e., mammals, humans, transgenic animals, etc), the Examiner suggests replacing the term with ---transformant cell--- to clearly indicate that the intended meaning of the term is a cell and not a multicellular organism.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The previous rejection of Claim 23 for reciting "so as to change the three-dimensional structure of the indicator or the expression vector of claim 22" is withdrawn by virtue of Applicants' amendment which deleted the phrase.

Claim 21 recites the phrase "a target sequence ..., wherein the target sequence is calmodulin" which is unclear and indefinite. A sequence is a graphical representation of a polypeptide, and as such, it cannot not be a protein such as calmodulin.

Claim 21 recites the phrase "substantially identical" which is unclear and indefinite. It is unclear what is encompassed by the "substantially identical" fluorescent properties. The term "substantially" in claim 21 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 21 recites the phrase "the donor fluorescent molecular component and the acceptor molecular component are fluorescent protein Venus," which is unclear and indefinite. It is unclear how both donor and acceptor fluorescent molecular components are the same protein, i.e., protein Venus.

Claim 21 recites the phrase "protein Venus," which is unclear and indefinite. The term "Venus" does not appear to be well known in the art or defined in the specification such that one of skill in the art could immediately envision the structure and/or function of a protein Venus. Based on the specification paragraph [0062], which states "Venus that is a YFP mutant can be used", the noted phrase is interpreted as any YFP mutant.

Claim 21 recites the phrase "the target sequence of the analytical substance," however there is insufficient antecedent basis for this limitation in the claim (see lines 3 and 7 of pg. 7).

Claim 21 recites the phrase "the target peptide," however there is insufficient antecedent basis for this limitation in the claim (see line 5 of pg. 7). It is noted by the Examiner that "the target peptide" is not the same as "a target peptide component".

Claim 21 recites the phrase "wherein the linker component allows the target sequence of the analytical substance to covalently fuse to the target peptide component, and the target sequence and the target peptide component covalently fuse to either the acceptor fluorescent molecular component or the donor fluorescent molecular component," which is unclear and indefinite. The noted phrase is so confusingly written that the Examiner cannot understand what it is that Applicants intend to claim as their invention.

Claim 21 recites the phrase, "wherein the analytical substance binding to the target sequence induces a change in the relative positions or directions of the target peptide component and the peptide-binding domain, and the relative positions or directions of the donor and acceptor molecular component undergo a change," which is

unclear and indefinite. The noted phrase is so confusingly written that the Examiner cannot understand what it is that Applicants intend to claim as their invention.

Due to the fact that the invention of claim 21 is very difficult to define because of many issues as discussed above, in the interest of advancing prosecution, the Examiner states his interpretation of claim 21 as "a polynucleotide encoding a polypeptide which can be used as a fluorescent indicator, wherein said polypeptide comprises calmodulin, a YFP mutant protein, skeletal muscle myosin light chain kinase (skMLCKp), and a linker component, wherein upon binding to an analytical substance, said polypeptide changes 3-D conformation."

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-23 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 21-23. In response to this rejection, Applicants have amended claims 21 and 23, and traverse the rejection as it applies to the newly amended claims.

Applicants submit that in order to advance prosecution of the application, and without expressing agreement or acquiescence to the rejection, claim 21 has been rewritten in independent form and elements of claims 2 to 6 have been added with focus on elected subject matter, such as calmodulin as target sequence, and skeletal muscle myosin light chain kinase (skMLCKp) as target peptide. Moreover, claim 21 has been amended to recite fluorescent protein Venus as fluorescent molecular component.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The instant claims are directed a broad genus of polynucleotides encoding any polypeptide which can be used as a fluorescent indicator, wherein said polypeptide comprises [1] a calmodulin, or optionally its fragments or variants thereof, which originated from any organism and does not necessarily have to have a biological function, [2] a YFP mutant protein, or optionally its fragments or variants thereof, which originated from any organism and does not necessarily have to have the same fluorescent properties associated with YFP (YFP mutant can have any biological function), [3] skeletal muscle myosin light chain kinase (skMLCKp), or optionally its fragments or variants thereof, which originated from any organism and does not necessarily have to have a biological function, and [4] any linker component, wherein upon binding to an analytical substance, said polypeptide changes 3-D conformation. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation. It is noted that such a broad genus of nucleic acids having essentially any structure and function is not supported by the instant application because the disclosure of the specification is limited to two representative species (see pg. 28 of the

specification), pRSET_B/W-cameleon obtained using primers, SEQ ID NOs: 40 and 41, and pRSET_B/W-SCAT obtained using primers, SEQ ID NOs: 42-45, with the template vector pRSET_B/Venus as disclosed in the reference of Nagai et al. (Nature Biotechnology, 2002, Vol. 20, pg. 97-90). However, these two disclosed species fail to provide adequate written description for the aforementioned genus.

In light of the notion that proteins having very different structures can have the same function (Kisselev et al, 2002), while proteins having very similar structure can have different activities (Witkowski et al, 1999; Wishart et al, 1995), one of skill in the art would not have recognized that Applicants were in possession of such a broad genus of polynucleotides encoding proteins having any biologically relevant functions, i.e., homo-FRET or the ability to fluorescence when an analytical substance binds or reacts, so that the proteins encoded by the claimed genus of nucleic acids can be used in FRET assays for the visualization of intermolecular interaction (see pg. 2, 2nd paragraph of the specification). For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for two vectors as disclosed on pg. 28 of the specification, pRSET_B/W-

cameleon obtained using primers, SEQ ID NOs: 40 and 41, and pRSET_B/W-SCAT obtained using primers, SEQ ID NOs: 42-45, with the template vector pRSET_B/Venus as disclosed in the reference of Nagai et al. (Nature Biotechnology, 2002, Vol. 20, pg. 97-90), does not reasonably provide enablement for (1) any polynucleotides encoding any polypeptides which can be used as a fluorescent indicator, wherein said polypeptides comprise [1] a calmodulin, or optionally its fragments or variants thereof, all of which originated from any organism and does not necessarily have to have a biological function, [2] a YFP mutant protein, or optionally its fragments or variants thereof, all of which originated from any organism and does not necessarily have to have a biological function, [3] skeletal muscle myosin light chain kinase (skMLCKp), or optionally its fragments or variants thereof, all of which originated from any organism and does not necessarily have to have a biological function, and [4] any linker component, wherein upon binding to an analytical substance, said polypeptide changes 3-D conformation; (B) an expression vector containing said polynucleotides; and (C) a transformant having said expression vector, as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 21-23. In response to this rejection, Applicants have amended claims 21 and 23, and traverse the rejection as it applies to the newly amended claims.

Applicants submit that in order to advance prosecution of the application, and without expressing agreement or acquiescence to the rejection, claim 21 has been

rewritten in independent form and elements of claims 2 to 6 have been added with focus on elected subject matter, such as calmodulin as target sequence, and skeletal muscle myosin light chain kinase (skMLCKp) as target peptide. Moreover, claim 21 has been amended to recite fluorescent protein Venus as fluorescent molecular component.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The instant claims are directed any polynucleotide encoding any polypeptide which can be used as a fluorescent indicator, wherein said polypeptide comprises [1] a calmodulin, or optionally its fragments or variants thereof, all of which originated from any organism and does not necessarily have to have a biological function, [2] a YFP mutant protein, or optionally its fragments or variants thereof, all of which originated from any organism and does not necessarily have to have a biological function, [3] skeletal muscle myosin light chain kinase (skMLCKp), or optionally its fragments or variants thereof, all of which originated from any organism and does not necessarily have to have a biological function, and [4] any linker component, wherein upon binding to an analytical substance, said polypeptide changes 3-D conformation. It is noted that such a broad scope of claimed polynucleotides, as described above in the 112 1st written description rejection, is not commensurate with the disclosure of the specification which is limited to two representative species (see pg. 28 of the specification), pRSET_B/W-cameleon obtained using primers, SEQ ID NOs: 40 and 41, and pRSET_B/W-SCAT obtained using primers, SEQ ID NOs: 42-45, with the template vector pRSET_B/Venus as disclosed in the reference of Nagai et al. (Nature Biotechnology, 2002, Vol. 20, pg. 97-90).

In light of the notion that proteins having very different structures can have the same function (Kisselev et al, 2002), while proteins having very similar structure can have different activities (Witkowski et al, 1999; Wishart et al, 1995), it would require undue experimentation for one of skill in the art to make and use the scope of inventions as claimed because one would have to determine which polynucleotides, out of essentially infinite number of possible polynucleotides having any structures, have the desired biological functions, i.e., homo-FRET or the ability to fluorescence when an analytical substance binds or reacts, so that they can be used in FRET assays for the visualization of intermolecular interaction. For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of (1) any polynucleotides encoding any polypeptides which can be used as a fluorescent indicator, wherein said polypeptide comprises [A] a calmodulin, or optionally its fragments or variants thereof, all of which originated from any organism and does not necessarily have to have a biological function, [2] a YFP mutant protein, or optionally its fragments or variants thereof, all of which originated from any organism and does not necessarily have to have a biological function, [3] skeletal muscle myosin light chain kinase (skMLCKp), or optionally its fragments or variants thereof, all of which originated from any organism and does not necessarily have to have a biological function, and [4] any linker component, wherein upon binding to an analytical substance, said polypeptide changes 3-D conformation, having the desired biological

characteristics, i.e., homo-FRET or the ability to fluorescence when an analytical substance binds or reacts, so that they can be used in FRET assays for the visualization of intermolecular interaction, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 21-23 are rejected under 35 U.S.C. § 102(b) as being anticipated by Nagai et al. (Circularly permuted green fluorescent proteins engineered to sense Ca^{2+} , PNAS, March 13, 2001, Vol. 98, No. 6, pg. 3197-3202).

The rejection was stated in the previous office action as it applied to previous claims 21-23. In response to this rejection, Applicants have amended claims 21 and 23, and traverse the rejection as it applies to the newly amended claims.

Applicants submit that in order to advance prosecution of the application, and without expressing agreement or acquiescence to the rejection, claim 21 has been rewritten in independent form and elements of claims 2 to 6 have been added with focus on elected subject matter, such as calmodulin as target sequence, and skeletal muscle myosin light chain kinase (skMLCKp) as target peptide. Moreover, claims 21 has been amended to recite fluorescent protein Venus as fluorescent molecular component.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. As previously indicated, Nagai et al. specifically teaches a fluorescent protein comprising calmodulin, YFP mutant at F46L, a 26-residue peptide derived from the calmodulin (CaM)-binding region of the skeletal muscle myosin light-chain kinase, and a linker, GlyGlySerGlyGly which undergoes 3-D conformation change in the presence or absence of an analytical substance, i.e., Ca^{2+} . As a result, the changes in fluorescence excitation and emission spectra of the fluorescent protein which are "direct effects of the Ca^{2+} -related structural change on the chromophore" (see the Examiner's interpretation of claim 21 above in 112 2nd paragraph rejection). As such, Nagai et al. anticipates the claimed invention which is drawn to "a polynucleotide encoding a polypeptide which can be used as a fluorescent indicator, wherein said polypeptide comprises calmodulin, YFP mutant protein, skeletal muscle myosin light chain kinase (skMLCKp), and a linker component, wherein upon binding to an analytical

substance, said polypeptide changes 3-D conformation." For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

The previous rejection of Claims 21-23 under 35 U.S.C. § 102(e) as being anticipated by Tsien et al. (Fluorescent protein sensors for detection of analytes, US Patent No. 5,998,204) is withdrawn because Tsien et al. do not teach a nucleic acid that encodes a YFP mutant or fluorescent protein Venus.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsien et al. (Fluorescent protein sensors for detection of analytes, US Patent No. 5,998,204).

Teachings of Tsien et al. are as described in the previous office action. In addition, Tsien et al. teach a linker moiety, i.e., Gly-Gly, (see claim 3). It is noted by the Examiner that the fluorescent indicator of Tsien et al. comprises GFP instead of YFP mutant (Venus), which is the only difference between the one taught by Tsien et al. and Applicants' fluorescent indicator as claimed. As such, it would have been obvious to one of skill in the art to swap GFP with another fluorescent protein such as YFP mutant

(Venus) because [1] they are art-recognized equivalent, and [2] their functions, i.e., acting as a fluorescent donor/acceptor, for the purpose of being used as a fluorescent indicator, are identical. Therefore, the claimed invention is prima facie obvious based on the teachings of Tsien et al.

The examiner has presented evidence to reasonably support that polynucleotides of prior art is encompassed by the claims. According to MPEP 2112.V, once a reference teaching a product appearing to be substantially identical is made the basis of a rejection, and the examiner presents evidence or reasoning tending to show inherency, the burden shifts to the applicant to show an unobvious difference.

Since the Office does not have the facilities for examining and comparing applicant's nucleic acid with the polynucleotides of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the polynucleotides of the prior art does not possess the same material structural and functional characteristics of the claimed nucleic acid). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

Double Patenting

Claims 21-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 5,998,204. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a nucleic acid sequence which

encodes a fluorescent indicator with overlapping scope in claimed nucleic acid sequence's structure and function.

It is noted by the Examiner that Applicants did not address this rejection in their remarks. As such, the rejection under this statute is maintained for the reasons of record.

Conclusion

Claims 21-23 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JAE W LEE/
Examiner, Art Unit 1656

/Delia M. Ramirez/

Delia M. Ramirez, Ph.D.
Primary Examiner, Art Unit 1652